J Biosci (2019) 44:22
DOI: 10.1007/s12038-018-9820-z

Review

Emerging roles of long non-coding RNAs in cancer

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MS received 18 September 2017; accepted 16 October 2018; published online 7 February 2019

Cancer is a physiological condition that has both the endogenous and exogenous influences on its progression. It originates from unusual cell growth, where the cells undergo massive genetic alterations, bypass the signaling machinery and compromise its genetic cohesion. Literature has well narrated the DNA damage studies including driver mutations that interfere with the treatment strategies. However, with evolving medical excellence, recent day studies are trying to unveil the contribution of RNAs in the progression of tumor malignancies. A number of non-coding RNAs have been identified as an active component in cancer genomics. This article aims to review the role of long non-coding RNAs in the spectra of cancers and its prognostic value as the biomarkers in molecular targeting with clinical utility and therapeutic beneficence.

Keywords. Biomarkers; cancers; DNA damages; genetic assaults; long non-coding RNAs; therapeutics

1. Introduction

Cancers are the result of genomic instability, where the genome integrity of a cell is compromised due to evasion of cell signaling pathways that otherwise regulates cell division, survival, proliferation, and senescence. The cells acquire irreparable damages, start dividing uncontrollably and transform into the malignant one. Cancer is the leading cause of the mortality and morbidity worldwide, accounting for about 14 million new registries in 2012 and 8.8 million deaths in 2015 (Stewart and Wild 2017). This estimates an incidence of 70% higher cancer risks in the next two decades. According to WHO 2017, five risk factors are found to be the cause of around one-third of the deaths. These are lack of physical activity, high body mass index, low intake of vegetables and fruits and the uses of tobacco and alcohol, where tobacco is responsible for 22% of the cancer deaths (Fitzmaurice *et al.* 2015).

Focusing into the physiological risk factors, genetic alterations may result from external influences like chemicals, radiation as well as pathogens (viruses) that disrupt the genome stability. Besides extensive studies on DNA damages in cell cycle regulation, past few decades evident the role of non-coding RNAs (ncRNAs) in the context of tumor biology. The existence of non-protein coding RNAs was known over years, where biological functions of these RNAs have been uncovered by progressive investigations (Palazzo and Lee 2015). Non-coding RNAs have further classifications, among which the functions of micro RNAs (miRNAs) have been thoroughly explored. Thus, we concentrate on the other type of ncRNA, the long non-coding RNAs (lncRNAs), a yet emerging field in the research of cancer biology. A fraction of the genome comprises these lncRNAs who are actually poorly translated as compared to other protein coding counterparts (Palazzo and Lee 2015). This paper aims to review the role of lncRNAs in a vast range of cancers with or without prognostic values and medical beneficence.

1.1 *Long non-coding RNAs in cancer regulation*

Recent studies have shown ncRNAs and miRNAs to have a pivotal role in regulating gene expression during development. Their involvement with a wide spectrum of human diseases, especially cancer is also documented well (Bertrand 2014; Adams *et al.* 2015). LncRNAs are transcripts of longer than 200 bp, poorly conserved, without or with mere protein-coding capacity (Qi and Du 2013). Human lncRNAs are transcribed by RNA polymerase II (RNA Pol II), polyadenylated and are spliced to generate short exonic regions (Tuncer and Bensan 2014; Bartonicek *et al.* 2016). They have important roles in cellular processes like transcriptional regulation, chromosome remodeling, post-translational modifications and disruption in them may lead to disease conditions (Bartonicek *et al.* 2016).

Recent studies focus on the functionality of lncRNAs in the meshwork of cancer pathways, where the lncRNAs are

found to have both oncogenic and tumor suppressing activity in regulating tumorigenesis (Beckedorff *et al.* 2013). The lncRNAs show tissue-specific expression property which is considered to be clinically beneficial for biomarker study; for example, prostate cancer shows high level of PCA3 (table 1) expression that serves as a prognostic marker in prostate cancer diagnosis. LncRNAs have diverged hold on oncogenic regulation, where it may directly interact with the mRNA splicing and translation or may also control the availability of micro RNAs needed for mRNA repression (Beckedorff *et al.* 2013; Tuncer and Bensan 2014).

Molecular mechanisms of lncRNAs denote the functionality of its different archetypes. It exhibits cell specificity and partakes in the signal transduction pathway by functioning as molecular signals. The transcriptional checkpoints are highly time-dependent and transmit regulatory clues to the targeted mechanism. A signal from DNA damage activates lncRNA p21 that targets p53 and induces apoptosis by functioning as a transcriptional repressor. It also represses p53 regulated genes on binding to it and modulating the localization of heterogeneous nuclear ribonucleoprotein k (hnRNP-K). Thus, the direct interaction of p53 with p21 promoter and induction of its expression gets altered upon reduction of lincRNA-p21. This DNA damage response, in turn, increases the expression of repressed-p53 transcripts (Wang and Chang 2011). The second archetype outlined the molecular decoys resulted from negative regulation of certain lncRNAs. The RNA binding proteins (RBPs) attached to these lncRNAs are demolished as the RNAs themselves function as transcriptional regulators or chromatin modifiers. They do not confer additional functions except deregulating the effectors and decaying the target proteins. Thus supports a loss of function of the effector. The mammalian MALAT1 localizes in the nuclear speckles and sequesters serine/arginine (SR) splicing factors to it. Depletion of MALAT1 rescues this mechanism leading to the release of splicing factor and activates alternative splicing. However, lncRNAs results in the rescue phenotype and a complete knock down may lead to a gain of function to the protein partner (Wang and Chang 2011). A similar function is observed by the circular RNA (circRNA) of transcription factor fork head box protein o3 (circ-foxo3) in cancer that interacts with cyclin-dependent kinase 2 (CDK2) and CDK inhibitor p21 and forms a tertiary cicr-foxo3-p21-CDK2 complex to inhibit cell cycle progression. This confers its ability to sequester RBPs to targeted complex and opens avenues in cancer therapeutics (Anastasiadou *et al.* 2018). The guide lncRNAs can regulate both the *cis (neighbouring genes)* and *trans* (distantly located genes) gene expressions by regulating the RBP-complexes and its interaction with targeted molecules. These regulatory lncRNAs can control chromatin remodeling in a co-transcriptional way (in *cis* guidance) or can bind to the target DNA as RNA-DNA heteroduplex and other conformational manners (in *trans*

Table 1. List of long non-coding RNAs associated with human cancers

Sl. No.	Terminologies	Abbreviations	Cancer types
1	Prostate cancer antigen 3	PCA3	Prostate cancer
2	X-inactive specific transcript	XIST	Breast cancer
3	HOX transcript antisense RNA	HOTAIR	Breast, cervical, Non small cell lung carcinoma
4	HOXA transcript at the distal tip	HOTTIP	Non small cell lung carcinoma
5	Prostate Cancer Associated Transcript 1	PCAT-1	Prostate cancer
6	C-terminal binding protein 1-AS region	CTBP1-AS	Prostate cancer
7	Antisense non-coding *RNA* in the RASSF1A locus	ANRASSF1	Breast cancer
8	Antisense noncoding RNA in the INK4 locus/ P15 antisense RNA	ANRIL/ p15AS	Non small cell lung carcinoma
9	Steroid receptor RNA activator	SRA	Colorectal carcinoma
10	Metastasis Associated Lung Adenocarcinoma Transcript 1	MALAT1	Hepatocellular carcinoma
11	colon cancer associated transcripts 1/2/6	CCAT1/2/6	Colorectal carcinoma
12	Growth arrest specific-5	GAS5	Breast cancer, Head and Neck cancers
13	Plasmacytoma variant translocation 1	PVT1	Colorectal carcinoma, Cervical cancer
14	Gastric carcinoma proliferation enhancing transcript 1	GHET1	Gastric cancer, Bladder cancer
15	Maternally expressed gene 3	MEG3	Prostate cancer, Lung cancer, Head and Neck cancers
16	*Taurine upregulated gene 1*	TUG1	Non small cell lung carcinoma
17	P21 associated ncRNA DNA damage activated	PANDA	Breast cancer
18	LncRNA activator of Enhancer Domains	LED	Several human cancers
19	Noncoding RNA activated by DNA damage	NOARD	Colorectal cancer
20	Prostate cancers identified Differential display 3	PCA3	Prostate cancer
21	SWI/SNF Complex Antagonist Associated With Prostate Cancer 1	SChLAP1	Prostate cancer
22	Telomeric repeat-containing *RNA*	TERRA	Aging and cancers
23	Nuclear Enriched Abundant Transcript 1	NEAT1	Prostate cancer

This table specifies the most likely studied lncRNAs and its expression sites of human carcinomas

guidance) (Wang and Chang 2011). HOTAIR is a classic example of *trans*-guidance lncRNA that regulates the chromatin modifier polycomb recessive complex 2 (PRC2) to the developmental HOXD locus, which if overexpressed in the cancer-related genes, may result into gene repression (Balas and Johnson 2018). XIST is another example of guide lncRNA that can recruit chromatin modifiers to loci those are specific for epigenetic means, where the XIST lncRNA facilitates X chromosome compensation; a phenomenon resulted from the ablated DNA and the XIST promoter (Bhat *et al.* 2016). The dynamic scaffold lncRNAs have several binding domains for the effector molecules including enzymatic complexes and other co-factors. A well-known example includes telomerase scaffold-RNA TERC. It combines the telomere RNA proteins with the reverse transcriptase activity in one ribonucleoprotein (RNP) and configures the telomerase complex required for protecting telomere end from gradual degradation (Wang and Chang 2011; Balas and Johnson 2018).

1.1.1 *LncRNAs in the transcriptional and translational control and cancer progression:* LncRNAs that takes part in transcriptional co-activation and repression also plays an important role in cancer epistasis. Such examples include the role of Linc-RNA-p21 in regulating p53 upon DNA damage and found to be upregulated in various tumor cell lines (Huarte *et al.* 2010). Similarly, studies by Yang *et al.* (2012) and Leygue *et al.* (1999) have shown the upregulation of H19 and SRA lncRNAs (Ref. table 1) in gastric and breast cancer cell lines respectively (Yang *et al.* 2012; Leygue *et al.* 1999). Post-transcriptional modifications involve MALAT1 (Ref. table 1), a well-studied lncRNA that controls alternative splicing by regulating the distribution of serine/arginine splicing factors (SR) and their protein levels in the nuclear speckles. MALAT1 is also found in high levels in various cancer tissues where it promotes cell motility and proliferation (Tripathi *et al.* 2010). Furthermore, loss of lncRNAs have also found in different cell homeostasis, such as PTENP1 (Ref. table 1), a pseudogene of PTEN tumor suppressor gene competes with miRNAs from binding with PTEN and controls its expression levels (Poliseno *et al.* 2010). HOXC locus transcribes HOTAIR and silences HOXD (Ref. table 1) locus by recruiting repressive complexes. HOTAIR was the first lncRNA to act on the other chromosome (*trans*) which redefines the role of lncRNAs, initially thought to act only on neighbouring genes (*cis*) only. LncRNAs are not only involved in assembling chromatin-modifying proteins but also have been found to participate in protein–DNA binding mechanism, building up the nuclear organization, translation and regulating mRNA levels. It can even modulate protein function through the capability of acting at multiple levels in the aspect of gene expression (Paralkar and Weiss 2013).

1.1.2 *Activation of lncRNAs on DNA damage response:* Cancer survivors with an underlined p53 mutation may not respond to chemotherapies due to impaired DNA damage repair mechanism. Example includes heterozygous, likely pathogenic, germline loss of functional Tp53 (c.323delG; p.Gly108ValfsTer15) to be related with a poor outcome with several malignancies in 8 out of 15 members from one Indian family affected with Li-Fraumeni syndrome; such cases of familial cancer syndromes make the treatment strategies even challenging (Chatterjee *et al.* 2016a, b). LncRNAs may play an important role in order to combat such novel cases (figure 1). TUG1 and PANDA are directly activated upon DNA damages and regulated by p53 for binding to their promoters, where their expressions are diminished in primary lung and breast tumors, respectively. TUG1 musters PRC2 to the promoter of HOXB7, lessening the HOX-mediated cell proliferation. PANDA binds to and revokes chromatin binding of NF-YA and represses apoptotic gene expression (Sahu *et al.* 2015). In addition to this, p53 also directs the enhancer RNAs (eRNAs), which function by altering the expression of neighbouring genes. LED (LncRNA activator of Enhancer Domains) has been identified as a p53-induced lncRNA that associates with activation of these remaining enhancers. LED is associated with the p21 enhancer and its knockdown results in G1 checkpoint arrest and thus supports cell survival. LED epigenetically deposits the active enhancer histone mark, H3K9ac and impacts eRNA production, while LED expression is found to be downregulated by hypermethylation in 44% of cancer cell lines. This suggests LED to be a p53-responsive

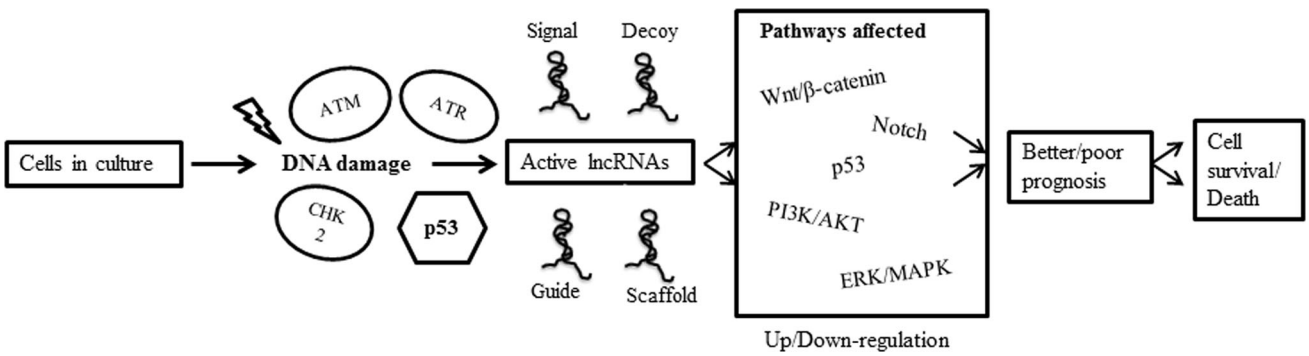

Figure 1. Schematic diagram of regulation of lncRNAs in DNA damage response.

lncRNA which regulates the p53 transcriptional response and serves tumor suppressive function as well (Sahu *et al.* 2015). Thus, it is well understood that a number of lncRNAs function as the gatekeepers of DNA damage repair mechanism, cell cycle progression, and apoptosis, where dysregulation of these RNAs may accelerate cell immortality.

NORAD (non-coding RNA activated by DNA damage) is a cytoplasmic ncRNA, that is highly expressed and conserved between mouse and human and is induced by DNA damage. It is found to be deleted in otherwise karyotypically stable human colon carcinoma. It results in aneuploidy with a marked increase in spontaneous tetraploidization that alters the genome integrity. NORAD binds to the Pumilio homolog (PUM) RNA-binding proteins that associate with specific mRNAs at their 3′ untranslated regions (UTRs) through Pumilio response elements and facilitates mRNA degradation. NORAD negatively regulates PUM2 function through multiple repetitive Pumilio-binding motifs, where overexpression of PUM1 or PUM2 induces aneuploidy and its knockdown in *NORAD−/−* cells rescues the chromosome instability phenotype. These evident that NORAD maintains chromosome stability by suppressing PUM activities which helps to explore the developmental and pathological significance of *Norad* in mouse models and in clinical studies (Lin and He 2017).

1.1.3 *Telomere biology and lncRNAs:* Another aspect of cancer biology focuses on telomere shortening, which otherwise protects the end of chromosomes from being degraded under normal cellular processes and provides chromosomal stability. Although telomeres are known to be transcriptionally silent, recent literature independently support that subtelomeric and telomeric regions are still capable to be transcribed into telomeric UUAGGG-repeat comprising of ncRNAs, also known as TERRA. In mammals, TERRA has been shown to efficiently inhibit telomerase activity *in vitro* by base pairing with the template region of the RNA component of telomerase. A study done by Caslini *et al.* (2009) has shown the involvement of TERRA in regulating transcriptional modulators. Like, an increased transcription of TERRA is associated with the regulation of functional cooperation between transcriptional regulator MLL and the tumor suppressor protein p53. This is upregulated via telomere uncapping either by knocking down TRF2 shelterin protein or by its exposure to telomere Gstrand DNA oligonucleotides. Another study by Sampl *et al.* (2012) has found out a negative correlation between the expressions of TERRA in patients with glioblastoma. The diagnostic finding of TERRA levels in astrocytoma WHO grade 2 to 4 corresponds to the advanced stages of human larynx, colon and lymph node tumors. However, much evidence is required to know the mechanism of how TERRA is expressed and the amount of TERRA transcripts are regulated in the cell.

However, in the context of medical oncology, lncRNAs play a major role as prognostic markers that determine the effect of various drugs on cancer treatment. Depending upon the cancer sites, the involvement of lncRNAs may reflect the suitable treatment strategies in the era of personalized therapies. Further illustrations focus on how the lncRNAs function in different cancer types and their benefit in translational research as a biomarker with clinical beneficence and prognostic values.

1.2 *LncRNAs in breast and gynaecological cancers*

Carcinoma of the mammary gland has taken major attention all around the globe. Clinical classification defines breast cancers depending on the estrogen receptor (ER), progesterone receptor (PR) and her2/neu receptor status as hormone receptor-positive, her2/neu receptor-positive and a triple negative breast cancer where the immunohistochemical analysis shows a complete absence of all the three receptors. However, luminal A, luminal B, HER2 enriched, claudin-low, basal-like and normal breast-like classifications are based on the global transcriptome analysis (Holliday and Speirs 2011). Besides breast carcinomas in females, male breast cancers too have taken over similar attention due to having mutations in the crucial genes. High throughput investigations by Chatterjee *et al.* (2016a, b) have shown mutations in BRCA2, BRIP1, PTEN, PI3KCA, NBN and RB1 genes in patients are associated with male breast cancers.

As the conventional serum biomarker analysis (CEA, CA125) limits the clinical utility, long non-coding RNAs have been identified as the potential biomarkers in finding therapeutic directions in breast cancer tissues bearing differential expression patterns (Qi *et al.* 2016). A study by Yang *et al.* (2016) has identified almost 1300 lncRNAs with significantly aberrant expression patterns in the HER-2 positive breast cancer. Similarly, Shen *et al.* (2015) has also found over 1750 lncRNAs with differential expression in triple negative breast cancer (TNBC). Moreover, this prognostic data helped in distinguishing TNBC from non-TNBC breast cancer types (Lv *et al.* 2016). In this way, the lncRNAs can be direct targets of ER in luminal A-like breast cancer cells and may also serve as predictive biomarkers.

H19, a well-known lncRNA, is greatly expressed in the extraembryonic tissue. After birth, its expression is repressed except in a few adult tissues, including mammary gland (figure 2). Upregulation of H19 is noticed in breast cancer, where it may also function as a Myc-upregulated gene to initiate tumorigenesis and is often associated with poor prognosis (Cerk *et al.* 2016).

The mechanism of action of mouse metastatic breast cancer involves regulation of epithelial-mesenchymal transition (EMT) and mesenchymal-epithelial transition (MET) by interfering with miR-200b/b and let-7b microRNAs. This, in turn, regulates tissue invasion and metastasis, where the expression of E-cadherin is diminished in EMT with elevated levels of N-cadherin, vimentin or fibronectin-like

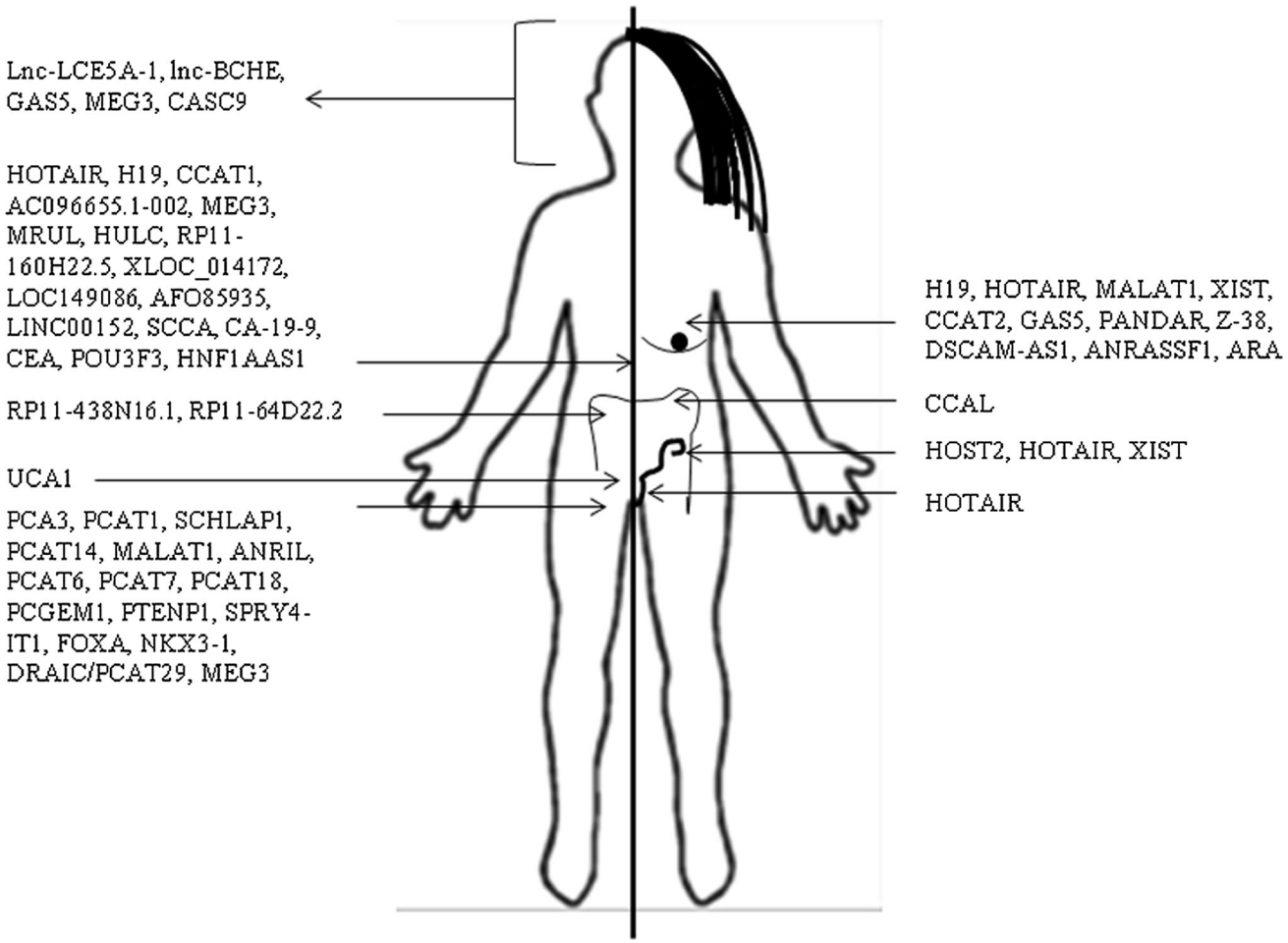

Figure 2. LncRNAs as prognostic markers in different cancer types: Long non-coding RNAs in different cancer sites are represented by arrows and detailed in the text.

mesenchymal markers (Collette *et al.* 2017; Zhang *et al.* 2017). H19 is also known as an active participant in the cell cycle regulation, where it undergoes c-myc-dependent transcription resulting in cell proliferation and breast oncogenesis. Upregulation of H19 lncRNA results into G1 to S cell cycle transition while its downregulation by RNAi blocks S phase entry and proliferation (Collette *et al.* 2017).

HOTAIR (homeobox (HOX) transcript antisense RNA) is the first identified lncRNA in human breast carcinoma. Estradiol transcriptionally induces HOTAIR by functional estrogen response elements and is thought to contribute to breast cancer progression (Bhan *et al.* 2013; Bhan and Mandal 2016) (figure 2). A study by Zhou *et al.* (2017) has studied radiosensitizing effects of HOTAIR, which shows its ability to induce radioresistance by inter-fering with the upregulation of HOXD10 and the PI3K/AKT-BAD signaling pathway. HOTAIR too is well involved in EMT where it elucidates the repression of E-cadherin by PRC2, while silencing of HOTAIR results in EMT abruption and stem cell production (Zhang *et al.* 2017).

Studies by several research groups have highlighted the pivotal role of MALAT1 in breast cancer prognosis. Xu *et al.* (2013) has established downregulation of MALAT-1 in breast tumor cell lines and in breast cancer tissue, where MALAT-1 regulates metastasis by activation of the phosphatidylinositide 3-kinase-protein kinase B (PI3K-AKT) pathway. Further study by Grembergen *et al.* (2016) has identified a remarkable difference between ER positive and negative breast tumors and an association of MALAT1 with ER status in malignancies (figure 2). In EMT, MALAT1 promotes the cellular transition and regulates cell migration, invasion and tumorigenesis, where studies evident high level of MALAT1 in breast cancer cells in comparison to the healthy ones (Zhang *et al.* 2017). A contradictory observation by Xu *et al.* (2015) reports the diminished expression of MALAT1 in breast cancer tissues; it shows knocking down of MALAT1 is associated with PI3K/AKT mediated EMT activation and breast cancer progression.

A study by Wu *et al.* (2016) has described differential co-expression of MALAT1 and XIST with *ALG14*, *TOX4* and *C12orf32* mRNAs in tumor and normal breast tissue via a *trans*-acting mechanism. XIST plays the key role of X-inactivation in females, whose expression has been found to be lost in female breast and gynaecological cancers (figure 2)

(Cerk *et al.* 2016). Redis *et al.* (2013) has studied the role of *CCAT2* in breast cancer, where it is found to be overexpressed with the highest expression in lymph node negative (LNN) condition. Expression levels are clinically informative for lymph node positive (LNP) disease that has received adjuvant CMF chemotherapy. This indicates that *CCAT2* may predict the metastasis and poor survival of LNPs similar to the expression of *HOTAIR lncRNAs.*

Another study done on human breast cancer reports GAS5 downregulation in breast cancer tissues possesses poor prognosis in cancer patients. Additionally, GAS5 promotes cell proliferation and/or apoptosis in breast cancer cells and acts as a tumor suppressor as well (figure 2). Li *et al.* (2016) has found a reduced level of GAS5 in trastuzumab-resistant breast cancer tissue taken from trastuzumab-treated patients. However, GAS5 knockdown promotes cell survival and tumor growth *in vivo* and its low level correlates with histological grade and advanced TNM stage which in turn indicates that GAS5 is lessened by trastuzumab and may act as a tumor suppressor in trastuzumab-resistant breast cancer (Cerk *et al.* 2016). DNA damage is a phenomenon, where the cells gain survival benefits if the repair mechanism fails in cellular recovery. In such cases, the expression of PANDAR is influenced by tumor protein p53. Silencing of this lncRNA results in DNA damage-induced cellular death and has control on cellular senescence as well.

Deng *et al.* (2016) has recently investigated that Z38 knockdown induces apoptosis by suppressing cell proliferation and tumorigenesis (figure 2). DSCAM-AS1 is an ER-dependent lncRNA and is antisense intronic within the DSCAM (Down Syndrome Cell Adhesion Molecule) gene, where DSCAM-AS1 knockdown mimics reduction of cellular growth and promotes apoptosis (Cerk *et al.* 2016). Another lncRNA, *ANRASSF1 (RASSF1 antisense RNA 1)* has been shown to be highly expressed in breast and prostate tumor cell lines, where RASSF1A was found to have an opposite pattern. *ARA (Adriamycin resistance associated)* is an intronic lncRNA, originated from the PAK3 intronic region and its expression is upregulated in breast cancer cell line upon adriamycin treatment (figure 2). ARA knockdown has also resulted in programmed cell death (Soudyab *et al.* 2016).

An additional mechanism of lncRNA in breast cancers highlights a recent study by Zhu *et al.* (2018), where the repetitive satellite RNAs in the heterochromatin region are found to be involved in DNA damage response, resulting in chromosomal instability and cell cycle regulation. The finding shows a possible interaction of BRCA1 associated protein networks with the Satellite RNAs that destabilizes the replication fork and results in genomic instability (Zhu *et al.* 2018).

Qi *et al.* (2016) has reviewed the status of *cervical cancer*, where the concentration of circulating lncRNAs has an implication on the disease state. HOTAIR is well-studied in interacting with Polycomb Repressive Complex 2 (PRC2) and trimethylated H3K27 at the HOXD gene locus, whose elevated level is an indication for tumor progression and metastasis (figure 2). Li *et al.* (2015) has measured a significant rise in HOTAIR expression in the serum of cervical cancer patients (Li *et al.* 2015).

Focusing on the *ovarian malignancies* that have the highest mortality rate worldwide, the human ovarian cancer (OC)-specific transcript 2 (HOST2) has been identified by Rangel *et al.*, in 2003, with a specific expression in EOC (Rangel et al. 2003). This has been found to be low or null in a spectrum of other common malignancies with great therapeutic benefits. HOTAIR knockdown has been shown to inhibit EMT and thus a reduced tumorigenesis is observed. Further studies indicate that reduction in XIST may affect the sensitivity of OC cells to Paclitaxel, suggesting XIST can serve as a biomarker in the prognosis of OC (figure 2). PVT1 is another lncRNA, whose amplification may result in cell survival being anti-apoptotic in nature. PVT1 is found to be associated with cisplatin resistance in OC (Zhong *et al.* 2016). Review by Zhan *et al.* (2018) highlights the role of H19 in epithelial ovarian cancer, where both the loss of heterozygosity and imprinting of H19 are associated with the disease progression. Interestingly, the underlined mechanism describes the similar EM transition found to promote cell invasion in other cancer types. The lncRNAs like MEG3 that facilitates differential gene expression confer significant association with the EMT-associated canonical pathways that involve the interaction of the ECM with specific receptors, focal adhesion and gap junctions (Mitra *et al.* 2017).

1.3 *Prognostic values of lncRNAs in gastrointestinal cancers (GI)*

It is the second highest cause of cancer-related mortality worldwide, where several research on the *carcinomas of the gastrointestinal system* have revealed around 135 lncRNAs to be associated with the disease state (Song *et al.* 2013; Xu *et al.* 2013). Among these, HOTAIR, H19, and CCAT1, like other cancer types, are found with higher expression patterns and have prognostic value in GI cancers (figure 2). However, few lncRNAs have shown to be downregulated in gastric cancers. Park *et al.* (2013) have shown downregulation of 31 differentially expressed tran-scripts including BM742401, which is associated with poor survival of GI patients. Another lncRNA found to be downregulated is AC096655.1–002 which has a great prognostic impression on the progression of GI cancers and a poor survival (Sun *et al.* 2013). An identical study has found reduced expression of MEG3 to be correlated with poor prognosis than those with relatively higher MEG3 expression (Jiang *et al.* 2014). In addition to this, Qi *et al.* (2016) have reviewed the role of reduced plasma Fer-1-Like Protein 4 (FER1L4), which when observed in patients, a keen decline in the expression has been noted two weeks after surgery. Wang

et al. (2014) has focused on the multidrug resistance (MDR) characteristic of gastric cancers that makes the patients resistant to the chemotherapy. Chemo regimens like doxorubicin (adriamycin [ADR]) and vincristine (VCR) has the ability to induce Bax- and Bak-mediated apoptosis via DNA damage. Moreover, *MRUL (M*DR-*r*elated and *u*pregulated *l*ncRNA) is another potential multidrug resistance-related lncRNA identified in gastric cancer patients (figure 2).

Concentrating on a more common type of gastrointestinal cancer, the *hepatocellular carcinoma (HCC)* or liver cancer, is globally the third most common cause of cancer-related deaths (Jemal *et al.* 2011; Llovet *et al.* 2012). HCC has its clinical limitation for its poor therapeutic response and increased risk of relapse after treatment (Hong *et al.* 2003; Fang *et al.* 2014). Among the lncRNAs, HULC (Highly Upregulated in Liver Cancer) has been found to be increased in the HCC and colorectal carcinomas that have a secondary liver metastasis (figure 2). Tang *et al.* (2015) identified upregulation of plasma RP11–160H22.5, XLOC_014172 and LOC149086 lncRNAs in HCC patients compared to that of control subjects. A combination of these three is found to have a better score for liver cancer diagnosis than that of individual lncRNA analysis. Additionally, lncRNAs XLOC_014172 and LOC149086 have benefits of having a prognostic value for metastasis prediction. A similar study has found serum AF085935 as a potent biomarker for HCC diagnosis (Qi *et al.* 2016).

Gallbladder cancer (GBC) is the fifth most frequent malignancy of the gastrointestinal system which is the most lethal cancers worldwide. It is usually detected at an advanced stage with a mean survival of fewer than six months and is still devoid of effective therapies. Several studies have documented the pivotal role of EMT in GBC progression, among which Zhao *et al.* (2015) has reported the involvement of LINC00152 in the EMT progression and induction of metastasis in gastric cancer. Further study by Cai *et al.* (2017) observed its positive effects on GBC cell migration, invasion, and EMT *in vitro* by manipulating LINC00152 expression. Moreover, further study has suggested the LINC00152/miR-138/HIF-1a signaling pathway regulatory network could be a novel therapeutic approach for patients with gallbladder cancers (figure 2) (Cai *et al.* 2017).

Another type of GI cancer is the esophageal squamous cell carcinoma (EC/ESCC) which is one of the most lethal types of digestive tract malignancy according to 2011 cancer statistics and has the most versatility in its prevalence all around the globe (Li *et al.* 2014a, b). Few identified biomarkers for EC are serum Squamous Cell Carcinoma Antigen (SCCA), CA19–9 and CEA which have a little clinical benefit in managing the patients (figure 2). Tong *et al.* (2015) has identified 10 ESCC-related lncRNAs in plasma, among which POU3F3, HNF1AAS1, and SPRY4-IT1 have been found in elevated levels in the patients' samples. Again, a combination of the measured lncRNAs showed better efficacy in detecting early-stage esophageal squamous cell carcinoma (Qi *et al.* 2016). GAS5 downregulation has been observed in the ESCC cells. A study by Ke *et al.* (2018) has observed overexpression of this lncRNA interferes with the ATM/CHK2 pathway and arrests cell cycle at the G2/M stage. Detailed insight into its mechanism has revealed increased levels of phosphorylated ATM, CHK2, CDK1 and CDC25C proteins upon transfected with pc-GAS5, whereas the unphosphorylated proteins show no significant difference under normal condition. Overexpression of GAS5 hence is found to be associated with EMT where it blocks cell migration by blocking the expressions of EMT-associated factors (Ke *et al.* 2018).

LncRNAs in GI cancers combine with the miRNAs and silence the targeted mRNAs during post-transcriptional regulations (Ji *et al.* 2016). This lncRNAs then act as a competing-endogenous RNA (ceRNA). Another molecular mechanism includes alternative splicing of pre-mRNA in the nuclear speckles regulated by lncRNAs in the presence of spliceosomal proteins and associated regulatory factors. Interestingly, colocalization of SF2/ASF is seen with MALAT1 in nuclear speckles, where MALAT1 regulates the recruitment of SF2/ASF and modulates its distribution to stimulate gastrointestinal malignancies (Chen *et al.* 2018).

1.4 *Role of lncRNAs in prostate cancer progression*

Prostate cancer (PCa) is the most common type of cancer in men with limitations in the molecular heterogeneity and accurate pathological interpretations of prostate tumors. Consecutive research on prostate cancer has identified few markers including TMPRSS2-ERG, PSCA, BRCA1/2, PTEN, KLK2, AMACR and TGFB. However, these markers do not procure a high prognostic value and are not accurate in predicting course of the disease. The first PCa-associated lncRNA discovered was highly expressed PCA3, located in the tumor-suppressive protein-coding gene PRUNE2 (figure 2). Loss of PCA3 results in compromised cell viability with a significant alteration in the androgen receptor (AR) target gene expressions (Li *et al.* 2014a, b; Bijnsdorp *et al.* 2017). Studies by Prensner *et al.* (2011, 2014) suggests PCa-associated transcript 1 (PCAT1) is a prostate-specific lncRNA that is found to be greatly upregulated in high-grade PCa (Gleason score C7), metastatic condition and in castration-resistant PCa (CRPC). Also, with respect to the expression, PCAT1 has an appreciative pattern than that of PCA3 and found to be active during DNA insults. It regulates BRCA2, controls *in vitro* homologous recombination and is sensitive to poly ADP ribose polymerase (PARP)-1 inhibitor *in vivo*. This has made PCAT1 a promising biomarker to predict response to PARP1 inhibition in the translational cancer therapeutics (Malik and Feng 2017; Qi *et al.* 2016). In addition, SCHLAP1 (second chromosome locus associated with prostate-1, a.k.a. PCAT11) has shown 25% overexpression in PCa and may interfere with diagnostic progression and cancer-specific death, becoming an antagonistic biomarker. One of the crucial mechanisms

involves androgen receptor (AR) sensitivity of the lncRNAs that facilitates AR signaling more efficiently than the endogenous enzyme. Androgen deprivation therapy (ADP) upregulates lncRNAs like HOTAIR supports negative regulation of lncRNAs by androgens. HOTAIR binds with the N-terminal domain of AR and prevents its ubiquitination and degradation by inhibiting the binding of ubiquitin ligase 3 MDM2 to it. Overexpression of this lncRNA may enhance AR-binding functionality and regulate transcriptional machinery in the absence of androgen (Aird *et al.* 2018). A study by Qi *et al.* (2016) have reported PCAT14 resistance to androgen-deprivation therapy (ADT). Moreover, several other lncRNAs, such as ANRIL, PCAT6, PCAT7, PCAT18, PCGEM1, PTENP1, and SPRY4-IT1 are found to be overly expressed in prostate tumors (Li *et al.* 2014a, b; Bijnsdorp *et al.* 2017). Ren *et al.* (2013) have reported MALAT1 overexpression results in poor prognosis in PCa. Malik and Feng (2016) state the downregulation of FOXA, NKX3-1, DRAIC/PCAT29 and MEG3 results in an advanced phenotype in prostate cancer (figure 2).

The second mechanism features the epigenetic modulation of lncRNAs in prostate cancers where it regulates DNA methylation, histone modifications and posttranscriptional regulations (Xu *et al.* 2018). Another important mechanism of action explains the role of lncRNA in EMT regulation of prostate cancer. LncRNAs like PCA3, CCAT2 are known to regulate the expressions of N-cadherin, E-cadherin, β-catenin, and vimentin like mesenchymal markers and facilitate cellular metastasis (Aird *et al.* 2018).

1.5 *LncRNAs in colorectal cancer (CRC)*

Colon cancer represents third most common cancer and the third leading cause of cancer death in the United States with a diminished disease incidence around the globe (Chen *et al.* 2016). Research has narrated a poor prognosis of CCAL in CRC stage II and III patients on treatment with or without leucovorin, levamisole or cisplatin and a compelling interaction between Wnt/β-catenin signaling pathway (Ma *et al.* 2016). In this, CCAL has been found to negatively regulate AP-2α and provide a way to Wnt signaling in colon cancers (Yang *et al.* 2017a, b). Another lncRNA, CRNDE binds and represses miR181a-5p that otherwise inhibits Wnt/β-catenin signaling pathway; its upregulation thus promotes the pathway to favour cellular proliferation in CRC (Ong *et al.* 2018). Disruption in the Wnt/β-catenin signaling leads to oncogenesis in CRC as the β-catenin disruption complex comprises of proteins like axin, different kinases, phosphatases and other activators required for Wnt/β-catenin pathway regulation (Yang *et al.* 2017a, b). However, some lncRNAs like FOXD2-AS1 regulates CRC progression via notch or *trans* EMT pathways. It enhances the expression of E-cadherin and diminishes the expressions of N-cadherin and snail proteins. Knocking down FOXD2-AS1 results in the decreased expression levels of Hes-1 and NICD marker proteins (Yang *et al.* 2017a, b). A study by Tsai *et al.* (2018) explains the role of Linc00659 in CRC via cell cycle mechanism, where silencing this lncRNA may lead to apoptosis by cleaving PARP and caspase-3; hence its disregulation or upregulation may contribute to CRC progression (Tsai *et al.* 2018).

1.6 *Non-small cell lung cancer (NSCLC) prognosis and LncRNAs*

NSCLCs comprises about 80% of diagnosed lung cancers with a limitation of long survival rate due to the late diagnosis and drug resistance in the targeted molecular therapies. The most altered genes in NSCLC progression are TP53, EGFR, and KRAS which provide key directions in the molecular drug targeting. The lncRNA, HOTAIR has been found to be upregulated and behave as a negative prognostic factor in lung carcinomas with a metastatic impression and a therapeutic benefit (Liu *et al.* 2013a, b). Moreover, in NSCLCs, upregulation of HOTAIR has resulted in cisplatin resistance by the regulation of p21. In contrast, downregulation of HOTAIR results into increased chemosensitivity that in turn promotes cell apoptosis (Liu *et al.* 2013a, b). NSCLCs also highlights the role of MALAT1 in their early stage metastasis and comparatively poor prognosis, where its knockdown in xenograft model has shown no metastasis of lung tumor, indicating MALAT1 to be a good molecular target in the treatment of non-small cell lung carcinomas (figure 2). The mechanism of action involves the alternative splicing where MALAT1 interacts with Serine/Arginine (SR) proteins and interferes with the gene expression. MALAT1 activates metastatic-related genes without affecting the alternative splicing machinery. However, its epigenetic mechanism explains the re-localization of growth control genes between polycomb bodies and interchromatin granules by the interaction of MALAT1 with demethylated PC2 protein molecule (Cheng and Mao 2017). Additional data suggests the loss of imprinting dependent overexpression of H19 in NSCLCs to be associated with exogenous risk factors including smoking, hypoxia and other exposure to environmental carcinogens (Kaplan *et al.* 2003). Matouk *et al.* (2010) have demonstrated the hypoxia-induced upregulation of H19 by MYC oncogene. They also have explained its interaction with p53 mutation through an HIF1-alpha factor that indicates H19 as a strong biomarker in lung carcinomas. Additionally, elevated expressions of MDIG and H19 have been found to result in poor survival of the lung cancer patients (Chen *et al.* 2013). Cheng and Mao (2017) have also reviewed the downregulation of MEG3 is associated with poor prognosis, whereas, its upregulation has resulted in induced cell death by activating p53 pathway. An interesting study done by Hu *et al.* (2016) has identified 21 lncRNAs associated with NSCLCs from plasma sample analysis, in which ANRIL has been reported with the

highest diagnostic beneficence. Furthermore, circulating SPRY4-IT1, ANRIL, and NEAT1 in combination may serve as a predictor for NSCLC as they are related to the tumor size, increase in the levels may stipulate a greater tumor burden in NSCLC tissues (figure 2) (Qi *et al.* 2016). NSCLC progression has also shown a significant relation with Wnt/β-catenin pathway where knockdown of CCAT2 results in arrested cell proliferation. Moreover, a significant reduction of proteins like c-myc, β-catenin and CCND1 are observed for the same. This clues a possible involvement of Wnt/β-catenin signaling in the CCND1-dependent cell metastasis in NSC lung carcinoma (Li *et al.* 2017).

1.7 *Head and neck carcinoma and prognosis of lncRNAs*

Head and neck squamous cell carcinoma (HNSCC) is the sixth leading cancer worldwide (Ferlay *et al.* 2010). Studies have identified 2808 transcripts express differentially including reduced regulation of lnc-LCE5A-1(∼112-fold in HNSCC) and a relative upregulation of (∼58-fold in HNSCC) lnc-BCHE RNAs (figure 2). In contrast, the expression level of GAS5 has not been considered as a significant data for HNSCC prediction. However, the tumor suppressor MEG-3 is involved in p53 activation and is downregulated in HNSCCs by less than two-fold (figure 2) (Zhang *et al.* 2009; Zou *et al.* 2015).

Focusing on the types of head and neck carcinoma, the laryngeal squamous cell carcinoma (LSCC) represents 4% of all the cancer types worldwide. LSCCs are mostly treated with laser resection, partial or total laryngectomy or radiation therapy; but, treatment based on personalized medicine is greatly needed to treat the voice disorders and dysphagia in advanced cases. In order to achieve such therapeutic advantages, identification of lncRNA-biomarkers is essential. A study by Feng *et al.* (2016) has identified1459 differentially expressed lncRNAs among which 846 are upregulated with an efficacy of differentiating tumor tissues from adjacent non-neoplastic tissues. Epigenetic mechanism emphasizes attenuation of the methylation state of PTEN by HOTAIR knockdown and the regulation of LSCC cell invasion. On the other way, HOTAIR regulates EMT by decreasing E-cadherin and governs the binding of the enhancer of zest homolog 2 (EZH2) and trimethylation of lysine 27 on histone 3 (H3K27me3) to the promoter of E-cadherin and inflates metastasis (Luo *et al.* 2018).

The second type describes *nasopharyngeal carcinoma (NPC)*, one of the promising head and neck malignancies that emerge from the epithelial cells in the nasopharynx. Su *et al.* (2017) have observed CASC9 be highly expressed in NPC tissues that promote cell growth and has a poor prognosis in NPCs (figure 2). The study group has also noticed CASC9 act as an oncogenic regulator via activation of HIF1a that too facilitate cell cycle progression by controlling glycolysis metabolism. Further investigation suggests a reduction in CASC9 blocks tumor progression indicating a way out in cancer therapeutics. In NPC, MALAT1 functions as a ceRNA, regulates miR-1/slug axis, and fosters redioresistance. It either regulates transcriptional events or expedites alternative splicing. As a ceRNA MALAT1 downregulates miR-1 that in turn increases the expression of slug protein and promotes the activity of cancer stem cells; thus stimulates the radioresistance in the NPC cells (Song *et al.* 2018). Downregulated MALAT1 subdues the EMT markers like N-cadherin and vimentin in HNC. It also modulates the Wnt/β-catenin pathway and promotes EMT, cell migration and invasion in tongue squamous cell carcinoma (TSCC) (Luo *et al.* 2018).

1.8 *Adrenocortical carcinoma (ACC) and lncRNAs*

ACC represents aggressive malignancy with limited treatment options and a survival rate of less than 35%. Among the lncRNAs involved, RP11–438N16.1 has been noted to be highly expressed with a fold change of 30.7 (figure 2). The maximum fold change observed is 94.5 for the lncRNA gene RP11–64D22.2 (figure 2) (Glover *et al.* 2015).

1.9 *Bladder cancer prognosis and the role of lncRNAs*

Bladder cancer has shown an upregulation of tissue-UCA1, where the circulating UCA1 have also been detected in blood and urine of few patients (figure 2). This marker is predominant in distinguishing bladder cancer from other urinary tract diseases, like the neurogenic bladder, renal cell carcinoma and upper urinary tract restriction or reflux with an overall specificity of 91.8%. Determination of UCA1 level in blood sample of bladder cancer patients indicates the effect of cisplatin-based combination therapy; likewise UCA1 may be used to determine the outcome of chemotherapy for bladder cancer (Fan *et al.* 2014; Qi *et al.* 2016). Further studies have documented microarray-based signal detection of 9,351 lncRNAs (Peter *et al.* 2014). A key lncRNA to induce bladder cancer cell proliferation is FOXD2-AS1. This regulates the kinase activity and PI3K-AKT signaling where silencing of FOXD2-AS1 leads to the alteration of the AKT downstream genes. FOXD2-AS1 is also observed to form a feedback loop with AKT-E2F1 that keeps the TRIB3/AKT pathway always activated in this cancer type. Thus FOXD2-AS1 lncRNA governs cell cycle by regulating E2F and contributes to bladder tissue malignancies (Su *et al.* 2018). In the mechanism of EMT, the lncRNAs interact with mRNA or miRNAs and facilitates tumorigenesis. Examples include the interaction of HOTAIR with ZEB1, MALAT with E-cadherin and UCA-1/ZEB1/2 (Pop-Bica *et al.* 2017).

2. Discussion

Carcinogenesis and tumor progression involves a meshwork of genes, proteins, and associated cellular components, where the cells are susceptible to acquire external hits and sustain an unusual phenotype. Study at the gene level underpinned the importance of translational research at this most evolving field of biology. Next generation sequencing has outlined the consequences of altered gene expressions, protein truncation and pathogenicity of several malignancies. However, it has limitations in huge data analysis, sensitivity and, specificity of the technique that has put molecular targeting at a most challenging stage. Identifications of large deletions or insertions, chromosomal fusions, chromothripsis or chromoplexy are the constraints that need more accuracy and data validation expertise (Berger *et al.* 2011; Alves *et al.* 2013; Shen 2013; Martens-Uzunova *et al.* 2014). However, biomarker identifications and molecular targeting have opened a new avenue in the field of cancer therapeutics. It eases the treatment strategies by locating the faulty genomic interactions inside the cell and indicates more specific targets for cell death. Discovery of long non-coding RNAs and their interactions with the oncogenic pathways serves the most precise information to the clinical aspect of cancer management. Elevated or diminished expression of lncRNAs in cancer cells have resulted in cell survival or apoptosis providing either a better or a poor prognosis. Studies have shown stress-induced activation of long non-coding RNA and transcriptional repression of heat shock genes with the formation of nuclear stress bodies in cervical cancer lines, which if extended may further impact the mechanistic role of such lncRNA in other cancers (Sengupta *et al.* 2009; Goenka *et al.* 2016). This review narrates about the most abundant lncRNAs that have crucial roles in regulating tumorigenesis. As discussed earlier, the lncRNAs function as different archetypes like signal, decoys, guide or scaffold in several types of cancers (Balas and Johnson 2018; Wang and Chang 2011; Anastasiadou *et al.* 2018; Bhat *et al.* 2016). Thus, the lncRNAs interact with the key regulatory proteins and participates in or modulates some crucial signaling pathways to regulate cancer progression. Such examples include regulation of p53 by lncRNA DINO (DNA damage induced non-coding), where DINO can stabilize p53, mimic the function of DNA damage-induced p53 and activates damage signaling and cell cycle arrest. Due to the formed auto-feedback loop, mdm2 is present to balance the cell toxicity effect produced by excess p53 induction. Similarly, LincRNA-p21 is the transcriptional target of p53 that acts as a repressor in p53-pathway, where PANDA regulates p53 dependent cell cycle and apoptosis (Peng *et al.* 2017). Concentrating in each cancer type, the breast and gynaecological cancers undergo EMT or the altered cell cycle regulation by H19, HOTAIR, and MALAT1 by targeting regulatory pathways like PI3K/AKT (Collette *et al.* 2017; Zhang *et al.* 2017). Treatment-dependent regulation of lncRNA has been observed in malignancies of mammary gland with noticeable therapeutic aspects. Example includes a study by Cerk *et al.* (2016) on GAS5 regulation upon treatment with trastuzumab in breast cancer. Interestingly, the satellite RNAs are found to take part in DNA damage response and cell cycle regulation that signifies its role in chromosome instability and oncogenesis (Zhu *et al.* 2018). Moving to the other gynaecological cancers, ovarian malignancies are also observed to be involved in the EMT machinery where H19, MEG3 have been found to play major roles in interacting with the adhesive molecules and cellular junctions. However, the mechanisms are still emerging and may find involvement of more lncRNAs over further investigations. In cancer signaling pathways, the growth factors interact with the receptor tyrosine kinase (RTK) and activate PIP_3 via PI3K which in turn activates the downstream targets like AKT. Thus PI3K and PTEN function as the key regulator of AKT. Moreover, few lncRNAs also regulate AKT in a direct or indirect manner. BC087858 is such an lncRNA that upregulates ZEB1 and snail proteins and governs EMT along with PI3K/AKT and MEK/ERK signaling pathways. Similarly, MALAT1 is found to activate PI3K/AKT pathway to induce tumorigenesis (Peng *et al.* 2017). Gastrointestinal malignancies have a spectrum of tumor types that give rise to cancers of the gallbladder, hepatic cells, esophageal squamous cells and more. Among multiple functions, GAS5 is also involved in GI carcinomas where it downregulates ESCC cells by interacting with the ATM/CHK2 pathway and promotes cell cycle arrest (Ke *et al.* 2018). Intriguingly, MALAT1 shows a different mechanism of action where it regulates the alternative splicing interacts with serine and arginine splicing factors and co-localize with it in the nuclear speckles (Chen *et al.* 2018). Such varied mechanistic proliferation of GI cancers has made the diagnosis more research-oriented and promising one. Epigenetic moderations like ubiquitination, histone modifications play important roles in prostate cancer (Aird *et al.* 2018; Xu *et al.* 2018). HOTAIR interacts with the androgen receptor and blocks its ubiquitination and protects it from MDM2-mediated degradation. Other lncRNAs like CCAT2, PCA3 undergoes EMT and regulates mesenchymal markers to promote cell growth (Aird *et al.* 2018). However, prostate cancer is one of the higher incidental cancer types needs more findings of accurate prognostic markers for its early detection. Focusing on the colorectal malignancies, the CCAL lncRNA interferes with the Wnt/ β-catenin signaling pathway and regulates cell survival (Yang *et al.* 2017a, b). Also, FOXD2-AS1 regulates the *trans*-EMT and modulates the proliferation and cell invasion of CRC tumorigenesis (Yang *et al.* 2017a, b). A study by Tsai *et al.* (2018) describes the effect of Linc00659 knockdown that leads to apoptosis by cleavage of regulatory caspases. Thus, genetic moderations upon drug administration may provide novel data in CRC prognosis. Abnormal lung tissue development includes

several genetic alterations where mutations in the p53, EGFR and KRAS have well-known impact in the disease progression. Several targeted therapies have been introduced depending upon the genetic profile of the lung cancer patients. However, the mechanism needs to be well understood as a number of lncRNAs are involved in regulating lung tumor cells. A similar alternative splicing approach is noticed by MALAT1 in GI cancers (Cheng and Mao 2017). Few other mechanisms involve hypoxia-induced H19 upregulation and the function of CCAT2 in the Wnt/ β-catenin dependent oncogenic transformation (Matouk *et al.* 2010; Li *et al.* 2017). As lung cancer has well-studied data, in-depth findings may reveal new molecular targets and therapeutic approaches. Cancers of the head and neck are also the results of similar mechanistic regulation where the cells undergo EMT or epigenetic changes. HOTAIR decreases the expression of E-cadherin by interacting with the intermediary molecules and promotes cell invasion (Luo *et al.* 2018). A different mechanism involves the induction of radioresistance in HNC cells by MALAT1 through the regulation of slug proteins (Song *et al.* 2018). Also, MALAT1 regulates both the EMT and Wnt signaling and establishes itself as an important regulator of head and neck cancers. Nevertheless, there are malignancies that need more insights to decipher their mechanism of action. Such example includes carcinoma of the adrenal cortex (Glover *et al.* 2015). The last section of this review highlights the findings in bladder cancer. In this, the FOXD2-AS1 lncRNA is involved in the PI3K/AKT signaling and regulates cell cycle by interacting with the E2F protein. Interestingly, EMT shows a co-participation of both the lncRNA and its interacting mRNA or miRNA in regulating cell migration. HOTAIR partners with ZEB1 and facilitates tumorigenesis (Pop-Bica *et al.* 2017). Such interactions are rare in other types of malignancies. However, a brief note about the other lncRNAs involved in cancer signaling pathways highlights the regulation of notch pathway by LUNAR1 lncRNA. Furthermore, c-Myc, one of the crucial proteins in the oncogenic events gets upregulated by PVT1 and fosters primary tumor formations. MALAT1 follows the Wnt/β catenin signaling pathway and directs an alternative splicing mechanism. It also regulates the EM transition and other pathways like PI3K/AKT, ERK/MAPK and leads to angiogenesis (Peng *et al.* 2017). It is well understood that the lncRNA expressions are more tissue-specific and differ with the wide spectrum of cancer types. The variable genetic profile in individuals with cancer toughens the diagnosis at an early stage. This, with the help of genomic data, could be simplified and decipherable in designing the therapeutic strategies. Genetic alterations limit the advantages of chemotherapies by making the cells resistant to certain drug combinations. Identifying the specific variation may devise the drug delivery in a more targetable manner and transfigure the therapy into more personalized one. However, the experimental challenges may be overcome in the near future by technical advancement (Uzunova *et al.* 2014). The rapid improvement in biomedical engineering and great medical excellence may pledge an early cancer diagnosis and provide the individuals with the right treatment at the right time to live a healthy and rich lifespan.

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